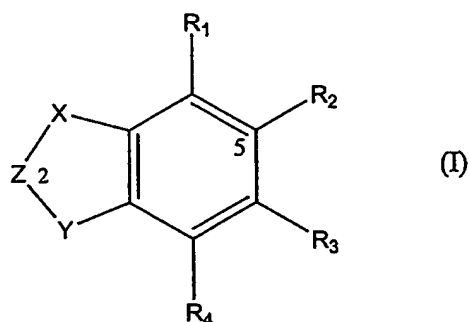


## CLAIMS:

1. A method of inhibiting cytokine or biological activity of MIF comprising contacting MIF with a cytokine or biological activity inhibiting effective amount of a  
 5 compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof



wherein

- 10 X is selected from -O-, -S-, -C(R<sub>5</sub>)(R<sub>5</sub>)- or -N(R<sub>6</sub>)-;

Y is selected from -N(R<sub>7</sub>)-, -O-, -S- or -C(R<sub>7</sub>)<sub>2</sub>-;

Z is selected from -C(O)-, -C(S)-, -C(=NR<sub>6</sub>)-, -S(O)- or -S(O)<sub>2</sub>-;

15

R<sub>1</sub> is selected from hydrogen, C<sub>1-3</sub>alkyl, (CR<sub>5</sub>R<sub>5</sub>)<sub>n</sub>OR<sub>7</sub>, (CR<sub>5</sub>R<sub>5</sub>)<sub>n</sub>SR<sub>7</sub>, (CR<sub>5</sub>R<sub>5</sub>)<sub>n</sub>N(R<sub>6</sub>)<sub>2</sub> and (CR<sub>5</sub>R<sub>5</sub>)<sub>n</sub>halo;

- 20 R<sub>2</sub> is selected from C<sub>1</sub>-C<sub>20</sub>alkyl, C<sub>2</sub>-C<sub>20</sub>alkenyl, C<sub>2</sub>-C<sub>20</sub>alkynyl, (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>C(O)R<sub>8</sub>, (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>C(S)R<sub>8</sub>, (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>S(O)R<sub>8</sub>, (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>S(O)<sub>2</sub>R<sub>8</sub>, (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>OR<sub>9</sub>, (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>SR<sub>9</sub>, (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>NR<sub>10</sub>R<sub>11</sub>, (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>C(=NR<sub>24</sub>)R<sub>22</sub> and (CR<sub>12</sub>R<sub>12</sub>)<sub>m</sub>R<sub>13</sub>;

- 25 R<sub>3</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, (CR<sub>16</sub>R<sub>16</sub>)<sub>p</sub>NR<sub>14</sub>R<sub>15</sub>, (CR<sub>16</sub>R<sub>16</sub>)<sub>p</sub>OR<sub>17</sub>, (CR<sub>16</sub>R<sub>16</sub>)<sub>p</sub>SR<sub>17</sub>, (CR<sub>16</sub>R<sub>16</sub>)<sub>p</sub>halo, (CR<sub>16</sub>R<sub>16</sub>)<sub>p</sub>NO<sub>2</sub>, (CR<sub>16</sub>R<sub>16</sub>)<sub>n</sub>C(O)R<sub>28</sub>, (CR<sub>16</sub>R<sub>16</sub>)<sub>n</sub>C(=NR<sub>24</sub>)R<sub>22</sub>, (CR<sub>16</sub>R<sub>16</sub>)<sub>n</sub>S(O)R<sub>17</sub>, (CR<sub>16</sub>R<sub>16</sub>)<sub>n</sub>S(O)<sub>2</sub>R<sub>17</sub>, (CR<sub>16</sub>R<sub>16</sub>)<sub>n</sub>S(O)<sub>3</sub>R<sub>17</sub> and (CR<sub>16</sub>R<sub>16</sub>)<sub>p</sub>C(R<sub>18</sub>)<sub>3</sub>;

$R_4$  is selected from hydrogen, halogen  $C_1$ - $C_3$ alkyl,  $C_2$ - $C_3$ alkenyl,  $C_2$ - $C_3$ alkynyl and  $(CR_{12}R_{12'})_n C(R_{18})_3$ ;

- 5 Each  $R_5$  and  $R_5'$  is independently selected from hydrogen,  $C_1$ - $C_3$ alkyl, halo,  $OR_7$ ,  $SR_7$  and  $N(R_6)_2$ ;

Each  $R_6$  is independently selected from hydrogen,  $C_1$ - $C_3$ alkyl and  $OR_7$ ;

- 10 Each  $R_7$  is independently selected from hydrogen and  $C_1$ - $C_3$ alkyl;

$R_8$  is selected from hydrogen,  $C_1$ - $C_{20}$ alkyl,  $C_2$ - $C_{20}$ alkenyl,  $C_2$ - $C_{20}$ alkynyl,  $OR_{19}$ ,  $SR_{19}$ ,  $N(R_{20})_2$ ,  $[NH-CH(R_{21})-C(O)]_q-OR_{29}$ , [sugar] $_q$  and  $(CR_{12}R_{12'})_t R_{13}$ ;

- 15  $R_9$  is selected from hydrogen,  $C_1$ - $C_{20}$ alkyl,  $C_2$ - $C_{20}$ alkenyl,  $C_2$ - $C_{20}$ alkynyl,  $(CR_{12}R_{12'})_t R_{13}$ ,  $C(O)R_{23}$ ,  $CO_2R_{23}$ ,  $C(S)R_{23}$ ,  $C(S)OR_{23}$ ,  $S(O)R_{23}$ ,  $S(O)_2R_{23}$ ,  $[C(O)CH(R_{21})NH]_q-R_{23}$  and [sugar] $_q$ ;

- $R_{10}$  and  $R_{11}$  are independently selected from hydrogen,  $C_1$ - $C_{20}$ alkyl,  $C_2$ - $C_{20}$ alkenyl,  
20  $C_2$ - $C_{20}$ alkynyl,  $(CR_{12}R_{12'})_m R_{13}$ ,  $C(O)R_{23}$ ,  $C(S)R_{23}$ ,  $S(O)R_{23}$ ,  $S(O)_2R_{23}$ ,  $[C(O)CH(R_{21})NH]_q-R_{23}$ , -[sugar] $_q$  and  $NHC(=NR_{25})-NH_2$ ;

Each  $R_{12}$  and  $R_{12'}$  is independently selected from hydrogen,  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl,  $OR_{24}$ ,  $SR_{24}$ , halo,  $N(R_{24})_2$ ,  $CO_2R_{24}$ , CN,  $NO_2$ , aryl or heterocyclyl;

25

$R_{13}$  is selected from  $OR_{25}$ ,  $SR_{25}$ , halo,  $N(R_{25})_2$ ,  $C(O)R_{31}$ , CN,  $C(R_{18})_3$ , aryl or heterocyclyl;

$R_{14}$  and  $R_{15}$  are independently selected from hydrogen,  $C_1$ - $C_3$ alkyl,  $OR_{17}$ ,  $(CR_{16}R_{16'})_p C(R_{18})_3$ ;

30

Each  $R_{16}$  and  $R_{16'}$  is independently selected from hydrogen,  $C_1$ - $C_3$ alkyl, halo,  $OR_{17}$ ,  $SR_{17}$  and  $N(R_{17})_2$ ;

- Each  $R_{17}$  is independently selected from hydrogen and  $C_1$ - $C_3$ alkyl;
- Each  $R_{18}$  is independently selected from hydrogen and halo;
- 5  $R_{19}$  and each  $R_{20}$  are independently selected from hydrogen,  $C_1$ - $C_{20}$ alkyl,  $C_2$ - $C_{20}$ alkenyl,  $C_2$ - $C_{20}$ alkynyl,  $(CR_{26}R_{26'})_iR_{27}$ ;
- $R_{21}$  is the characterising group of an amino acid;
- 10  $R_{22}$  is selected from  $C_1$ - $C_6$ alkyl,  $NH_2$ ,  $NH(C_{1-6}alkyl)$ ,  $N(C_{1-6}alkyl)_2$ ,  $OR_{29}$  or  $SR_{29}$ ;
- $R_{23}$  is selected from hydrogen,  $C_1$ - $C_{20}$ alkyl,  $C_2$ - $C_{20}$ alkenyl,  $C_2$ - $C_{20}$ alkynyl, aryl  $(CR_{26}R_{26'})_iR_{27}$ ;
- 15 Each  $R_{24}$  is independently selected from hydrogen and  $C_1$ - $C_6$ alkyl;
- Each  $R_{25}$  is independently selected from hydrogen,  $C_1$ - $C_6$ alkyl,  $C_{1-3}alkoxyC_{1-3}alkyl$ , aryl and heterocyclyl;
- 20 Each  $R_{26}$  and  $R_{26'}$  is independently selected from hydrogen,  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl,  $OR_{29}$ ,  $SR_{29}$ , halo,  $N(R_{29})_2$ ,  $CO_2R_{29}$ ,  $CN$ ,  $NO_2$ , aryl and heterocyclyl;
- $R_{27}$  is selected from hydrogen,  $OR_{30}$ ,  $SR_{30}$ , halo,  $N(R_{30})_2$ ,  $CO_2R_{30}$ , aryl and heterocyclyl;
- 25  $R_{28}$  is selected from hydrogen,  $C_{1-6}alkyl$ ,  $OR_{29}$ ,  $SR_{29}$  or  $N(R_{29})_2$ ;
- Each  $R_{29}$  is independently selected from hydrogen and  $C_1$ - $C_3$ alkyl;
- 30 Each  $R_{30}$  is independently selected from hydrogen,  $C_1$ - $C_3$ alkyl, aryl and heterocyclyl;

$R_{31}$  is selected from  $C_{1-3}$ alkyl, OH,  $C_{1-3}$ alkoxy, aryl, aryloxy, heterocyclyl and heterocyclyloxy;

$n$  is 0 or an integer from 1 to 3;

5  $m$  is 0 or an integer from 1 to 20;

$p$  is 0 or an integer from 1 to 6;

$q$  is an integer from 1 to 5;

$t$  is an integer from 1 to 10;

10 wherein alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

2. A method according to claim 1 wherein X is selected from the group consisting of -N(H)-, -N( $C_{1-3}$ alkyl)-, -N(OH)-, -N(OC $_{1-3}$ alkyl)-, -O-, -S-, -CH<sub>2</sub>-, -CH(OH)-, -CH(NH<sub>2</sub>)-, -CH( $C_{1-3}$ alkyl)-, -CH(halo)-, -CH(SH)-, -CH(OC $_{1-3}$ alkyl)-, -CH(SC $_{1-3}$ alkyl)-.

15

3. A method according to claim 1 wherein Y is selected from the group consisting of -NH-, -O-, -S-, -N( $C_{1-3}$ alkyl)- or -CH<sub>2</sub>-.

4. A method according to claim 1 wherein Z is selected from the group consisting of  
20 -C(O)-, -C(S)-, -C(=NH)-, -C(=NC $_{1-3}$ alkyl)-, -C(=NOH)- or -C(=NOC $_{1-3}$ alkyl)-.

5. A method according to claim 1 wherein  $R_1$  is selected from the group consisting of hydrogen, CH<sub>3</sub>, OH, SH, NH<sub>2</sub>, NHCH<sub>3</sub>, F, Cl or Br.

25 6. A method according to claim 1 wherein  $R_2$  is selected from the group consisting of  $C_{1-20}$ alkyl,  $C_{1-20}$ alkenyl,  $(CR_{12}R_{12'})_m$ heterocyclyl,  $(CR_{12}R_{12'})_m$ aryl,  $(CR_{12}R_{12'})_m$ halo,  $(CR_{12}R_{12'})_m$ OH,  $(CR_{12}R_{12'})_m$ OC $_{1-20}$ alkyl,  $(CR_{12}R_{12'})_m$ OC $_{2-20}$ alkenyl,  $(CR_{12}R_{12'})_m$ OC(O) $C_{1-20}$ alkyl,  $(CR_{12}R_{12'})_m$ OC(O) $C_{2-20}$ alkenyl,  $(CR_{12}R_{12'})_m$ OC(O)aryl,  $(CR_{12}R_{12'})_m$ O[C(O)CH( $R_{21}$ )NH] <sub>$r$</sub> -H,  $(CR_{12}R_{12'})_m$ O[sugar] <sub>$r$</sub> ,  $(CR_{12}R_{12'})_m$ NH<sub>2</sub>,  $(CR_{12}R_{12'})_m$ NHC $_{1-20}$ alkyl,  $(CR_{12}R_{12'})_m$ N( $C_{1-20}$ alkyl)<sub>2</sub>,  $(CR_{12}R_{12'})_m$ NHC $_{2-20}$ alkenyl,  $(CR_{12}R_{12'})_m$ N( $C_{2-20}$ alkenyl)<sub>2</sub>,  $(CR_{12}R_{12'})_m$ N( $C_{1-20}$ alkyl)( $C_{2-20}$ alkenyl),  $(CR_{12}R_{12'})_m$ NHC(O) $C_{1-20}$ alkyl,  $(CR_{12}R_{12'})_m$ NHC(O) $C_{2-20}$ alkenyl,  $(CR_{12}R_{12'})_m$ NHC(O)aryl,  
30

$(\text{CR}_{12}\text{R}_{12'})_m\text{NH}[\text{C}(\text{O})\text{CH}(\text{R}_{21})\text{NH}]_r\text{H}$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{NH}[\text{sugar}]_r$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{SO}_3\text{H}$ ,  
 $(\text{CR}_{12}\text{R}_{12'})_m\text{SO}_3\text{C}_{1-20}\text{alkyl}$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{SO}_3\text{C}_{2-20}\text{alkenyl}$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})\text{C}_{1-20}\text{alkyl}$ ,  
 $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})\text{C}_{2-20}\text{alkenyl}$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{CO}_2\text{H}$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{CO}_2\text{C}_{1-20}\text{alkyl}$ ,  
 $(\text{CR}_{12}\text{R}_{12'})_m\text{CO}_2\text{C}_{2-20}\text{alkenyl}$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})\text{NHC}_{1-20}\text{alkyl}$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})\text{N}(\text{C}_{1-20}\text{alkyl})_2$ ,  
 $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})\text{NHC}_{2-20}\text{alkenyl}$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})\text{N}(\text{C}_{2-20}\text{alkenyl})_2$ ,  
 $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})\text{N}(\text{C}_{1-20}\text{alkyl})(\text{C}_{2-20}\text{alkenyl})$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})[\text{NHCH}(\text{R}_{21})\text{C}(\text{O})]_r\text{OH}$ ,  
 $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})[\text{NHCH}(\text{R}_{21})\text{C}(\text{O})]_r\text{OCH}_3$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{C}(\text{O})[\text{sugar}]_r$ ,  $(\text{CR}_{12}\text{R}_{12'})_m\text{SC}_{1-6}\text{alkyl}$ ,  $\text{C}(=\text{N})\text{NHC}_{1-6}\text{alkyl}$ ; wherein each  $\text{R}_{12}$  and  $\text{R}_{12'}$  is independently selected from  
hydrogen,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{C}_{2-6}\text{alkynyl}$ , halogen, OH, hydroxy $\text{C}_{1-6}\text{alkyl}$ ,  $\text{OC}_{1-6}\text{alkyl}$ ,  
10  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{C}_{1-3}\text{alkyl}$ ,  $\text{NH}_2$ ,  $\text{NHC}_{1-3}\text{alkyl}$ ,  $\text{N}(\text{C}_{1-3}\text{alkyl})_2$ , CN,  $\text{NO}_2$ , aryl or heterocyclyl;  $\text{R}_{21}$   
is the characterising group of an amino acid,  $m$  is 0 or an integer from 1 to 20 and  $r$  is an  
integer from 1 to 5.

7. A method according to claim 1 wherein  $\text{R}_3$  is selected from the group consisting of  
15 hydrogen, halogen,  $\text{C}_1\text{-C}_6\text{alkyl}$ ,  $-(\text{CH}_2)_n\text{NH}_2$ ,  $-(\text{CH}_2)_n\text{NO}_2$ ,  $-(\text{CH}_2)_n\text{OH}$ ,  $-(\text{CH}_2)_n\text{CF}_3$  or  
 $-(\text{CH}_2)_n\text{SH}$  wherein  $n$  is as defined in claim 1.

8. A method according to claim 1 wherein  $\text{R}_4$  is selected from the group consisting of  
hydrogen, methyl, ethyl,  $-\text{CH}_2=\text{CH}_2$ ,  $\text{CH}_2\text{CF}_3$ , fluoro, chloro or bromo.

20 9. A method according to claim 1 wherein at least one of  $\text{R}_5$  and  $\text{R}_{5'}$  in each  $(\text{CR}_5\text{R}_{5'})$   
is hydrogen.

10. A method according to claim 1 wherein at least one of  $\text{R}_{12}$  and  $\text{R}_{12'}$  in each  
25  $(\text{CR}_{12}\text{R}_{12'})$  is hydrogen.

11. A method according to claim 1 wherein at least one of  $\text{R}_{16}$  and  $\text{R}_{16'}$  in each  
 $(\text{CR}_{16}\text{R}_{16'})$  is hydrogen.

30 12. A method according to claim 1 wherein at least one of  $\text{R}_{26}$  and  $\text{R}_{26'}$  in each  
 $(\text{CR}_{26}\text{R}_{26'})$  is hydrogen.

13. A method according to claim 1 wherein

X is selected from the group consisting of -O-, -S-, -C(R<sub>5</sub>)<sub>2</sub>- or -N(R<sub>6</sub>)<sub>2</sub>-;

5

Y is selected from the group consisting of -N(R<sub>7</sub>)<sub>2</sub>-, -O-, -S-, or -C(R<sub>7</sub>)<sub>2</sub>-;

Z is selected from the group consisting of -C(O)-, -C(S)-, -S(O)- or -C(=NR<sub>6</sub>)<sub>2</sub>-;

10 R<sub>1</sub> is selected from the group consisting of hydrogen, CH<sub>3</sub>, OH, SH, NH<sub>2</sub>, NHCH<sub>3</sub>, F, Cl or Br;

R<sub>2</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>20</sub>alkyl, C<sub>2</sub>-C<sub>20</sub>alkenyl, C<sub>2</sub>-C<sub>20</sub>alkynyl, (CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>C(O)R<sub>8</sub>, -(CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>C(S)R<sub>8</sub>, -(CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>S(O)R<sub>8</sub>, -(CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>S(O)<sub>2</sub>R<sub>8</sub>, -  
 15 (CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>OR<sub>9</sub>, -(CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>SR<sub>9</sub>, -(CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>NR<sub>10</sub>R<sub>11</sub>, (CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>C(=NR<sub>24</sub>)R<sub>22</sub> or (CR<sub>12</sub>R<sub>12'</sub>)<sub>m</sub>R<sub>13</sub> where m, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>12'</sub>, R<sub>13</sub>, R<sub>22</sub> and R<sub>24</sub> are as defined in claim 1;

R<sub>3</sub> is hydrogen, halogen, C<sub>1-6</sub>alkyl, -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NO<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-OH, -(CH<sub>2</sub>)<sub>n</sub>CF<sub>3</sub> or -  
 20 (CH<sub>2</sub>)<sub>n</sub>SH where n is as defined in claim 1; and

R<sub>4</sub> is hydrogen, halogen, methyl, ethyl, CH<sub>2</sub>CF<sub>3</sub> or -CH<sub>2</sub>=CH<sub>2</sub>.

14. A method according to claim 1 wherein

25 X is -N(R<sub>6</sub>)<sub>2</sub>-;

Y is -N(R<sub>7</sub>)<sub>2</sub>- or -C(R<sub>7</sub>)<sub>2</sub>-;

Z is -C(O)-, -C(S)-, -S(O)- or -C(=NH)<sub>2</sub>;

30

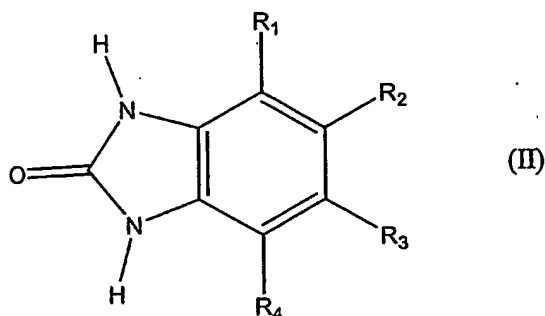
R<sub>1</sub> is hydrogen, CH<sub>3</sub>, NH<sub>2</sub>, NHCH<sub>3</sub>, F, Cl or Br;

$R_2$  is as defined in claim 1;

$R_3$  is hydrogen, halogen,  $C_{1-3}$ alkyl,  $(CH_2)_nNH_2$ ,  $-(CH_2)_nNO_2$ ,  $(CH_2)_nOH$  or  $(CH_2)_nCF_3$   
 5 where  $n$  is defined in claim 1; and

$R_4$  is hydrogen, halogen, methyl, ethyl,  $CH_2CF_3$  or  $-CH_2=CH_2$ .

15. A method according to claim 1 wherein the compound of formula (I) is a  
 10 benzimidazole compounds having the formula (II):



wherein

15

$R_1$  is hydrogen,  $CH_3$ ,  $NHCH_3$ , F, Cl or Br;

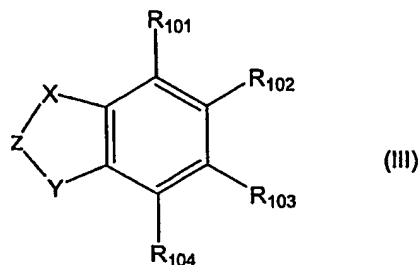
$R_2$  is as defined in claim 1;

20  $R_3$  is hydrogen, halogen,  $C_1-C_3$ alkyl,  $(CH_2)_nNH_2$ ,  $-(CH_2)_nNO_2$ ,  $(CH_2)_nOH$ ,  $CH_2C(O)CH_3$ ,  
 or  $(CH_2)_nCF_3$  where  $n$  is as defined in claim 1; and

$R_4$  is hydrogen, F, Cl or Br, methyl, ethyl,  $CH_2CF_3$  or  $-CH_2=CH_2$ .

25 16. A method according to claim 1 wherein the compound of formula (I) is a  
 compound of formula (III):

121



wherein

5

X is -O-, -NH- or -CH<sub>2</sub>-;

Y is -NH-, -O-, -S- or -CH<sub>2</sub>-;

10 

Z is -C(O)-, -C(S)- or -S(O)-;

R<sub>101</sub> is selected from hydrogen, C<sub>1-3</sub>alkyl, OH, SH, NH<sub>2</sub>, NHC<sub>1-3</sub>alkyl, F, Cl or Br;

15 R<sub>102</sub> is selected from C<sub>1-20</sub>alkyl, C<sub>2-20</sub>alkenyl, CO<sub>2</sub>H, CO<sub>2</sub>R<sub>105</sub>, -NH<sub>2</sub>, F, Cl, Br, (CH<sub>2</sub>)<sub>w</sub>R<sub>106</sub>,  
C(O)N(R<sub>107</sub>)<sub>2</sub>, C(=N)NHC<sub>1-6</sub>alkyl, SO<sub>2</sub>C<sub>1-6</sub>alkyl, C(O)[NHCH(R<sub>108</sub>)C(O)]<sub>q</sub>-OR<sub>109</sub>,  
C(O)sugar, CONH(CH<sub>2</sub>)<sub>n</sub>aryl, NHC(O)(CH<sub>2</sub>)<sub>n</sub>Sheterocyclyl, C(O)SC<sub>1-6</sub>alkyl,  
C(O)(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H, SO<sub>2</sub>OC<sub>1-10</sub>alkyl, and SO<sub>2</sub>NHC<sub>1-10</sub>alkyl;

20 R<sub>103</sub> is selected from hydrogen, F, Cl, Br, C<sub>1-6</sub>alkyl, -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NO<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-OH,  
-(CH<sub>2</sub>)<sub>n</sub>-CF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>C(O)C<sub>1-3</sub>alkyl or -(CH<sub>2</sub>)<sub>n</sub>-SH;

R<sub>104</sub> is selected from hydrogen, methyl, ethyl, CH<sub>2</sub>C(R<sub>110</sub>)<sub>3</sub>, C(R<sub>110</sub>)<sub>3</sub>, -CH<sub>2</sub>=CH<sub>2</sub>, fluoro,  
chloro or bromo;

25 R<sub>105</sub> is selected from hydrogen, C<sub>1-20</sub>alkyl, C<sub>2-20</sub>alkenyl or (CH<sub>2</sub>)<sub>t</sub>OC<sub>1-3</sub>alkyl;

R<sub>106</sub> is selected from SH, SC<sub>1-6</sub>alkyl, OH, OC<sub>1-6</sub>alkyl, sugar, CO<sub>2</sub>H, NH<sub>2</sub>, heterocyclyl or

aryl;

Each  $R_{107}$  is independently selected from hydrogen,  $C_{1-20}$ alkyl,  $C_{2-20}$ alkenyl,  $(CH_2)_t$ aryl and  $(CH_2)_t$ heterocyclyl;

5

$R_{108}$  is the characterising group of an amino acid;

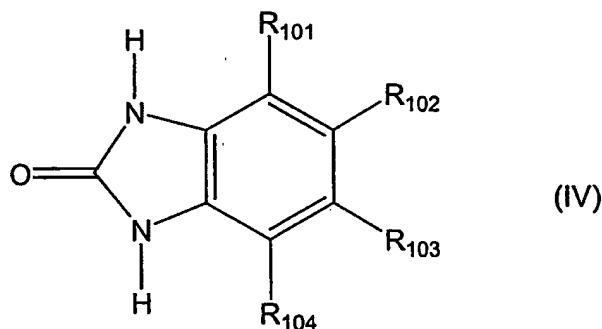
$R_{109}$  is hydrogen,  $C_{1-3}$ alkyl;

10 Each  $R_{110}$  is independently selected from hydrogen and halo; and

$n$  is 0 or an integer from 1 to 3,  $q$  is an integer from 1 to 5,  $w$  is an integer from 1 to 6;  $t$  is an integer from 1 to 10; wherein each alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

15

17. A method according to claim 1 wherein the compound of formula 1 is a compound of formula (IV):



20 wherein

$R_{101}$  is selected from hydrogen,  $CH_3$ , OH, SH,  $NH_2$ ,  $NHCH_3$ , F, Cl or Br;

$R_{102}$  is selected from  $C_{1-20}$ alkyl,  $C_{2-20}$ alkenyl,  $CO_2H$ ,  $CO_2R_{105}$ ,  $-NH_2$ , F, Cl, Br,  $(CH_2)_wR_{106}$ ,  
 25  $C(O)N(R_{107})_2$ ,  $C(=N)NHC_{1-6}$ alkyl,  $SO_2C_{1-6}$ alkyl,  $C(O)[NHCH(R_{108})C(O)]_q-OR_{109}$ ,  
 $C(O)sugar$ ,  $CONH(CH_2)_n$ aryl,  $NHC(O)(CH_2)_n$ heterocyclyl,  $C(O)SC_{1-6}$ alkyl,

$C(O)(CH_2)_nCO_2H$ ,  $SO_2OC_{1-10}alkyl$ , and  $SO_2NHC_{1-10}alkyl$ ;

$R_{103}$  is selected from hydrogen, F, Cl, Br,  $C_{1-6}alkyl$ ,  $(CH_2)_nNH_2$ ,  $-(CH_2)_nNO_2$ ,  $-(CH_2)_n-OH$ ,  $-(CH_2)_n-CF_3$ ,  $CH_2C(O)CH_3$  or  $-(CH_2)_n-SH$ ;

5

$R_{104}$  is selected from hydrogen, methyl, ethyl,  $CH_2CF_3$ ,  $-CH_2=CH_2$  fluoro, chloro or bromo;

$R_{105}$  is selected from hydrogen,  $C_{1-10}alkyl$ ,  $C_{2-10}alkenyl$ ,  $(CH_2)_tOC_{1-3}alkyl$ ;

10

$R_{106}$  is selected from  $SH$ ,  $SC_{1-6}alkyl$ ,  $OH$ ,  $OC_{1-6}alkyl$ , sugar,  $CO_2H$ ,  $NH_2$ , heterocyclyl or aryl;

Each  $R_{107}$  is independently selected from hydrogen,  $C_{1-10}alkyl$ ,  $C_{2-10}alkenyl$ ,  $(CH_2)_taryl$  and  $(CH_2)_theterocyclyl$ ;

15

$R_{108}$  is the characterising group of an amino acid;

$R_{109}$  is hydrogen,  $C_{1-3}alkyl$ ;

20

Each  $R_{110}$  is independently selected from hydrogen and halo; and

$n$  is 0 or an integer from 1 to 3,  $q$  is an integer from 1 to 5,  $w$  is an integer from 1 to 6,  $t$  is an integer from 1 to 10; wherein each alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

25

18. A method according to claim 1 wherein the compound of formula 1 is selected from the group consisting of:

benzimidazole-2-one-5-n-pentanoate,

30

5-[2-(1-oxy-2-hydroxyethyl)ethyl]benzimidazol-2-one-5-carboxylate,

benzimidazole-2-one-5-methanoate,

- benzimidazole-2-one-5-ethanoate,  
 3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]tetrahydro-2H-pyran-2-yl-  
 benzimidazole-2-one-5-carboxylate,  
 5-bromo-6-methylbenzimidazol-2-one,  
 5-hydroxy-6-methylbenzimidazol-2-one,  
 5-dodecanylbenzoimidazol-2-one,  
 4,5,7-tribromo-6-methylbenzimidazol-2-one,  
 4,5,6,7-tetrabromobenzimidazol-2-one,  
 5-methyl-6-nitrobenzimidazol-2-one,  
 5-amino-6-methylbenzimidazol-2-one,  
 N-(6-methylbenzimidazol-5-yl)-2-pyrimidin-2-yl-sulfanyl-acetamide,  
 pentyl-benzimidazol-2-one-5-carbothioate,  
 5-(benzimidazol-2(3H)-one-6-yl)-5-oxopentanoic acid,  
 2(3H)-benzimidazolone-5-sulfonic acid pentyl ester,  
 2(3H)-benzimidazolone-5-sulfonic acid pentyl amide,  
 N-butyl-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboximidamide,  
 5-heptanoylbenzofuran-2(3H)-one,  
 methyl 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino} propanoate,  
 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino} propanoic acid,  
 methyl 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoate,  
 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoic acid, and  
 N-(3,4-dihydroxyphenethyl)-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboxamide.

19. A method of treating, preventing or diagnosing a disease or condition wherein MIF  
 cytokine or biological activity is implicated comprising the administration of a treatment,  
 prevention or diagnostic effective amount of a compound of formula (I) as defined in claim  
 1 or a pharmaceutically acceptable salt or prodrug thereof to a subject in need thereof.

20. A method according to claim 19 wherein the disease or condition is selected from autoimmune diseases, solid or haemopoitic tumours and chronic or acute inflammatory diseases.

5

21. A method according to claim 19 wherein the disease or condition is selected from the group consisting of Rheumatic diseases, spondyloarthropathies, crystal arthropathies, Lyme disease, connective tissue diseases, vasculitides, glomerulonephritis, interstitial nephritis, inflammatory bowel disease, peptic ulceration, gastritis, oesophagitis, liver  
10 disease, autoimmune diseases, pulmonary diseases, cancers whether primary or metastatic, atherosclerosis, disorders of the hypothalamic-pituitary-adrenal axis, brain disorders, corneal disease, iritis, iridocyclitis, cataracts, uveitis, sarcoidosis, diseases characterised by modified angiogenesis, endometrial function, psoriasis, endotoxic (septic) shock, exotoxic (septic) shock, infective (true septic) shock, other complications of infection, pelvic  
15 inflammatory disease, transplant rejection, allergies, allergic rhinitis, bone diseases, atopic dermatitis, UV(B)-induced dermal cell activation, malarial complications, diabetes mellitus, pain, inflammatory consequences of trauma or ischaemia, testicular dysfunctions and wound healing.

20 22. A method according to claim 21 wherein the disease or condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, reactive arthritis, Reiter's syndrome, gout, pseudogout, calcium pyrophosphate deposition disease, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, Sjögren's syndrome, polyarteritis nodosa, Wegener's granulomatosis,  
25 Churg-Strauss syndrome, ulcerative colitis, Crohn's disease, cirrhosis, hepatitis, diabetes mellitus, thyroiditis, myasthenia gravis, sclerosing cholangitis, primary biliary cirrhosis, diffuse interstitial lung diseases, pneumoconioses, fibrosing alveolitis, asthma, bronchitis, bronchiectasis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, colon cancer, lymphoma, lung cancer, melanoma, prostate cancer, breast cancer, stomach  
30 cancer, leukemia, cervical cancer and metastatic cancer, ischaemic heart disease, myocardial infarction, stroke, peripheral vascular disease, Alzheimer's disease, multiple sclerosis, diabetic retinopathy, parturition, endometriosis, osteoporosis, Paget's disease,

sunburn and skin cancer.

23. A method of claim 19 wherein the subject is a human subject.

5 24. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier, diluent or excipient

25. A pharmaceutical composition according to claim 24 further comprising a  
10 glucocorticoid.

26. A method of treating or preventing a disease or condition wherein MIF cytokine or biological activity is implicated comprising:

15 administering to a mammal a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof and a second therapeutic agent.

27. A method according to claim 26 wherein the second therapeutic agent is a glucocorticoid.

20

28. A method of prophylaxis or treatment of a disease or condition for which treatment with a glucocorticoid is indicated, said method comprising:

administering to a mammal a glucocorticoid and a compound of formula (I) as  
25 defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof.

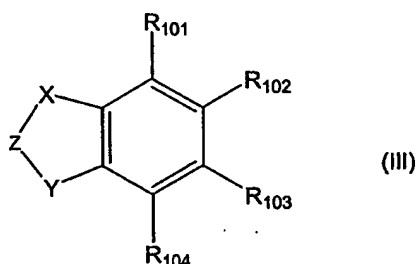
29. A method of treating a steroid-resistant disease or condition comprising:

administering to a mammal a glucocorticoid and a compound of formula (I) as  
30 defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof.

30. A method of enhancing the effect of a glucocorticoid in mammals comprising administering a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof simultaneously, separately or sequentially with said glucocorticoid.

5

31. A compound of formula (III) or a pharmaceutically acceptable salt or prodrug thereof:



10

wherein

X is -O-, -NH- or -CH<sub>2</sub>-;

15

Y is -NH-, -O-, -S- or -CH<sub>2</sub>-;

Z is -C(O)-, -C(S)- or -S(O)-;

R<sub>101</sub> is selected from hydrogen, C<sub>1-3</sub>alkyl, OH, SH, NH<sub>2</sub>, NHC<sub>1-3</sub>alkyl, F, Cl or Br;

20

R<sub>102</sub> is selected from C<sub>1-20</sub>alkyl, C<sub>2-20</sub>alkenyl, CO<sub>2</sub>H, F, Cl, Br, CO<sub>2</sub>R<sub>105</sub>, (CH<sub>2</sub>)<sub>w</sub>R<sub>106</sub>, C(O)N(R<sub>107</sub>)<sub>2</sub>, C(=N)NHC<sub>1-6</sub>alkyl, SO<sub>2</sub>C<sub>1-6</sub>alkyl, C(O)[NHCH(R<sub>108</sub>)C(O)]<sub>q</sub>-OR<sub>109</sub>, NH<sub>2</sub>, C(O)sugar, CONH(CH<sub>2</sub>)<sub>n</sub>aryl, NHC(O)(CH<sub>2</sub>)<sub>n</sub>Sheterocyclyl, C(O)SC<sub>1-6</sub>alkyl, C(O)(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H, SO<sub>2</sub>OC<sub>1-10</sub>alkyl and SO<sub>2</sub>NHC<sub>1-10</sub>alkyl;

25

R<sub>103</sub> is selected from hydrogen, F, Cl, Br, C<sub>1-6</sub>alkyl, -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NO<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-OH, -(CH<sub>2</sub>)<sub>n</sub>-CF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>C(O)C<sub>1-3</sub>alkyl or -(CH<sub>2</sub>)<sub>n</sub>-SH;

$R_{104}$  is selected from hydrogen, methyl, ethyl,  $\text{CH}_2\text{C}(\text{R}_{110})_3$ ,  $\text{C}(\text{R}_{110})_3$ ,  $-\text{CH}_2=\text{CH}_2$ , fluoro, chloro or bromo;

- 5  $R_{105}$  is selected from hydrogen,  $\text{C}_{1-20}$ alkyl,  $\text{C}_{2-20}$ alkenyl or  $(\text{CH}_2)_t\text{OC}_{1-3}$ alkyl;

$R_{106}$  is selected from SH,  $\text{SC}_{1-6}$ alkyl, OH,  $\text{OC}_{1-6}$ alkyl, sugar,  $\text{CO}_2\text{H}$ ,  $\text{NH}_2$ , heterocyclyl or aryl;

- 10 Each  $R_{107}$  is independently selected from hydrogen,  $\text{C}_{1-20}$ alkyl,  $\text{C}_{2-20}$ alkenyl,  $(\text{CH}_2)_t$ aryl and  $(\text{CH}_2)_t$ heterocyclyl;

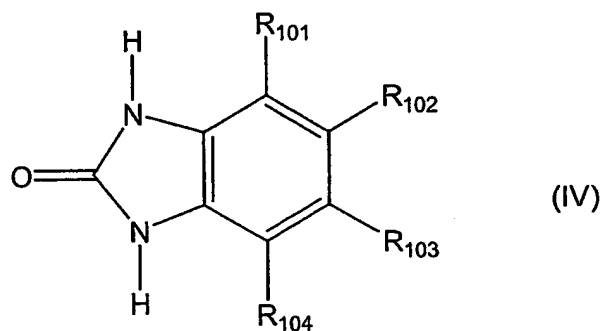
$R_{108}$  is the characterising group of an amino acid;

- 15  $R_{109}$  is hydrogen,  $\text{C}_{1-3}$ alkyl;

Each  $R_{110}$  is independently selected from hydrogen and halo; and

- 20 n is 0 or an integer from 1 to 3, q is an integer from 1 to 5, w is an integer from 1 to 6; t is an integer from 1 to 10; wherein each alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

32. A compound of formula (IV) or a pharmaceutically acceptable salt or prodrug thereof:



wherein

R<sub>101</sub> is selected from hydrogen, CH<sub>3</sub>, OH, SH, NH<sub>2</sub>, NHCH<sub>3</sub>, F, Cl or Br;

- 5 R<sub>102</sub> is selected from C<sub>1-20</sub>alkyl, C<sub>2-20</sub>alkenyl, CO<sub>2</sub>H, F, Cl, Br, CO<sub>2</sub>R<sub>105</sub>, (CH<sub>2</sub>)<sub>w</sub>R<sub>106</sub>, C(O)N(R<sub>107</sub>)<sub>2</sub>, C(=N)NHC<sub>1-6</sub>alkyl, SO<sub>2</sub>C<sub>1-6</sub>alkyl, C(O)[NHCH(R<sub>108</sub>)C(O)]<sub>q</sub>-OR<sub>109</sub>, NH<sub>2</sub>, C(O)sugar, CONH(CH<sub>2</sub>)<sub>n</sub>aryl, NHC(O)(CH<sub>2</sub>)<sub>n</sub>Sheterocyclyl, C(O)SC<sub>1-6</sub>alkyl, C(O)(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H, SO<sub>2</sub>OC<sub>1-10</sub>alkyl and SO<sub>2</sub>NHC<sub>1-10</sub>alkyl.
- 10 R<sub>103</sub> is selected from hydrogen, F, Cl, Br, C<sub>1-6</sub>alkyl, (CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NO<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-OH, -(CH<sub>2</sub>)<sub>n</sub>-CF<sub>3</sub>, CH<sub>2</sub>C(O)CH<sub>3</sub> or -(CH<sub>2</sub>)<sub>n</sub>-SH;

R<sub>104</sub> is selected from hydrogen, methyl, ethyl, CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>=CH<sub>2</sub> fluoro, chloro or bromo;

15

R<sub>105</sub> is selected from hydrogen, C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, (CH<sub>2</sub>)<sub>t</sub>OC<sub>1-3</sub>alkyl;

R<sub>106</sub> is selected from SH, SC<sub>1-6</sub>alkyl, OH, OC<sub>1-6</sub>alkyl, sugar, CO<sub>2</sub>H, NH<sub>2</sub>, heterocyclyl or aryl;

20

Each R<sub>107</sub> is independently selected from hydrogen, C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, (CH<sub>2</sub>)<sub>t</sub>aryl and (CH<sub>2</sub>)<sub>t</sub>heterocyclyl;

R<sub>108</sub> is the characterising group of an amino acid;

25

R<sub>109</sub> is hydrogen, C<sub>1-3</sub>alkyl;

Each R<sub>110</sub> is independently selected from hydrogen and halo; and

- 30 n is 0 or an integer from 1 to 3, q is an integer from 1 to 5, w is an integer from 1 to 6, t is an integer from 1 to 10; wherein each alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

33. A compound according to claim 32 wherein  $R_{101}$  is hydrogen, F, Cl or Br.
34. A compound according to claim 32 wherein  $R_{102}$  is  $C_{1-20}$ alkyl, halogen,  $NH_2$ ,  
 5  $CO_2H$ ,  $CO_2C_{1-10}$ alkyl,  $C(O)$ sugar,  $CO_2(CH_2)_nOC_{1-6}$ alkyl,  $CONHC_{1-10}$ alkyl,  
 $CONH(CH_2)_n$ aryl,  $CO[NHCH(R_{107})CO]-OH$ ,  $CO[NHCH(R_{107})CO]OC_{1-3}$ alkyl,  
 $NHC(O)(CH_2)_n$ Sheterocyclyl,  $C(O)SC_{1-6}$ alkyl,  $C(O)(CH_2)_nCO_2H$ ,  $SO_2OC_{1-10}$ alkyl,  
 $SO_2NHC_{1-10}$ alkyl or  $C(=NH)NHC_{1-6}$ alkyl.
- 10 35. A compound according to claim 32 wherein  $R_{103}$  is hydrogen, halogen,  $C_{1-3}$ alkyl,  
 $(CH_2)_nNH_2$ ,  $(CH_2)_nNO_2$ ,  $(CH_2)_nNH_2$ ,  $(CH_2)_nOH$  or  $(CH_2)_nCF_3$ .
36. A compound according to claim 32 wherein  $R_{104}$  is hydrogen, F, Cl or Br.
- 15 37. A compound according to claim 32 wherein  $R_{107}$  is the characterising group from  
serine ( $CH_2OH$ ) or phenylalanine ( $CH_2Ph$ ).
38. A compound of formula (I) selected from the group consisting of:  
benzimidazole-2-one-5-n-pentanoate,  
20 5-[2-(1-oxy-2-hydroxyethyl)ethyl]benzimidazol-2-one-5-carboxylate,  
benzimidazole-2-one-5-methanoate,  
benzimidazole-2-one-5-ethanoate,  
3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]tetrahydro-2H-pyran-2-yl-  
benzimidazole-2-one-5-carboxylate,  
25 5-bromo-6-methylbenzimidazol-2-one,  
5-hydroxy-6-methylbenzimidazol-2-one,  
5-dodecanylbenzoimidazol-2-one,  
4,5,7-tribromo-6-methylbenzimidazol-2-one,  
4,5,6,7-tetrabromobenzimidazol-2-one,  
30 5-methyl-6-nitrobenzimidazol-2-one,  
5-amino-6methylbenzimidazol-2-one,

- N-(6-methylbenzimidazol-5-yl)-2-pyrimidin-2-yl-sulfanyl-acetamide,  
 pentyl-benzimidazol-2-one-5-carbothioate,  
 5-(benzimidazol-2(3H)-one-6-yl)-5-oxopentanoic acid,  
 2(3H)-benzimidazolone-5-sulfonic acid pentyl ester,  
 5 2(3H)-benzimidazolone-5-sulfonic acid pentyl amide,  
 N-butyl-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboximidamide,  
 5-heptanoylbenzofuran-2(3H)-one,  
 methyl 3-hydroxy-2-{{{(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-  
 yl)carbonyl]amino}propanoate,  
 10 3-hydroxy-2-{{{(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-  
 yl)carbonyl]amino}propanoic acid,  
 methyl 2-{{{(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-  
 phenyl propanoate,  
 2-{{{(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl  
 15 propanoic acid, and  
 N-(3,4-dihydroxyphenethyl)-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-  
 carboxamide.